REMARKS

Applicants respectfully request entry of the amendments presented herein. These amendments place the application in better condition for allowance or in better form for appeal, and raise no new issues. Claims 37 and 43-55 stand rejected. Claim 37 is amended herein to recite hydroxyethylstarch-protein conjugate, characterized in that the binding interaction between the hydroxyethylstarch molecule and the protein is a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group of the hydroxyethylstarch molecule and (ii) a primary amino group of the protein to form a Schiff's base. Claims 43-49 are amended for consistency with amended claim 37. Support for these amendments can be found, for example, in claim 50, which is cancelled herein without prejudice. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 37, 43-49, and 51-55.

Information Disclosure Statement

The Examiner stated that because the Information Disclosure Statement filed on June 25, 2007, was not accompanied by a statement as specified in 37 C.F.R. § 1.97(e), it was not considered. Applicants respectfully direct the Examiner to 37 C.F.R. § 1.97(c):

> An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of any of a final action under § 1.113, a notice of allowance under § 1.311, or an action that otherwise closes prosecution in the application, and it is accompanied by one of: (1) The statement specified in paragraph (e) of this section; or (2) The fee set forth in § 1.17(p). (Emphasis added.)

Since the Information Disclosure Statement filed on June 25, 2007, was accompanied by the fee set forth in 37 C.F.R. § 1.17(p), the statement under 1.97(e) is not required. Thus, Applicants respectfully request consideration of the references listed on the Form PTO-1449 filed on June 25, 2007.

Double Patenting

The Examiner maintained the provisional rejection of claims 37, 43-53, and 55 on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 37-50, 54, 56 and 74-78 of copending Application No. 10/506,366 (Publication No. US 2006/0217293). Assignee's agent submits herewith a Terminal Disclaimer under 37 C.F.R. §§ 3.73(b) and 1.321(b). In light of the above, Applicants respectfully request withdrawal of the provisional rejection of claims 37, 43-49, 51-53, and 55.

Rejections under 35 U.S.C. § 112

The Examiner maintained the rejection of claims 37 and 43-55 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleged that the specification does not disclose a representative number of HAS polysaccharides that can be conjugated to any protein, that the specification does not disclose functional derivatives or fragments of proteins, and that the examples do not describe selective amino bond formation with primary amines.

Applicants respectfully disagree. The previously claimed conjugates were fully described. To further prosecution, however, Applicants have amended the claims to recite hydroxyethylstarch- (HES-) protein conjugates. As noted in Applicants' response filed on July 6, 2007, Examples 11-15 at pages 26-28 of the specification disclose that high and low molecular weight HES was coupled to albumin, asparaginase, interleukin-2, and insulin, and a person of skill in the art reading these examples would have understood that the coupling in each case occurred via a Schiff's base, since in each case a reducing agent (sodium cyanoborohydride ($NaBH_3CN$) or sodium borohydride ($NaBH_4$)) was added to the reaction mixture. Thus, Applicants' specification discloses a representative number of the presently claimed conjugates

With respect to the Examiner's comment regarding functional derivatives and fragments, Applicants note that the specification at page 11, lines 7-14 discloses that the term "functional derivative or fragment" means a derivative or fragment that retains a desired biological property or activity of he parent molecule in whole or in part, and that antibody fragments are examples of such molecules. Further, regarding the Examiner's statement with respect to primary amines, it

appears that the Examiner believes the term "primary amino" to relate solely to the terminal amino group of a protein. Applicants note, however, that a primary amino ($-NH_2$) group can be present not only as a terminal amino group of a protein, but also in lysine and asparagine side-chains, for example. See, e.g., page 17, lines 11-15. Thus, the Examples describe amine bond formation with primary amines.

Given the above, a person of skill in the art at the time the application was filed would have appreciated that Applicants invented and were in possession of the presently claimed conjugates. Thus, Applicants respectfully request withdrawal of this rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph.

The Examiner maintained the rejection of claims 37 and 43-55 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner alleged that undue experimentation would be required to make and use the claimed HAS protein conjugates, "due to the unpredictability based on the different unknown structures of materials, such as the genus of hydroxyalkyl starch polysaccharides, the functional groups on the hydroxyalkyl starch polysaccharide, [and] the functional group[s] on the protein that are being used to conjugate the polysaccharide with the protein." The Examiner further asserted that without direction as to "whether the protein identified can tolerate the modifications contemplated a non-functional HAS-protein conjugate may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims."

Applicants respectfully disagree. The previous recited conjugates were fully enabled. To further prosecution, however, the claims have been amended to recite HES-protein conjugates. No undue experimentation would have been required for a person of skill in the art at the time Applicants filed to make and use the presently recited conjugates.

First, with respect to the Examiner's allegation regarding the "unknown structures" of the recited conjugates, Applicants note that the claims require the covalent bonding to be the result of a coupling reaction between (i) the terminal aldehyde group of the HES molecule and (ii) a primary amino group of the protein. Applicants further note that non-oxidized HES has only one aldehyde group (i.e., the terminal aldehyde group). In addition, the product of the coupling reaction is recited to be a Schiff's base. Thus, a skilled artisan would clearly have been guided to

choose reaction parameters such that the (only) aldehyde group of HES would react with an amino group of the protein. Further, the numerous examples (e.g., Examples 11-15) set forth in Applicants' specification provide sufficient information and guidance with regard to the necessary reaction conditions for forming a Schiff's base. Taken together, the features of the claims and the teaching contained in Applicants' specification define the reaction products and the reaction parameters.

Further, no undue experimentation would have been required for a skilled artisan to assess the function of the presently recited conjugates. For example, a person of skill in the art would have been able to test the function of the non-modified protein using any method known in the art for assessing the specific function of the protein, and to test the modified protein according to the same method. Such methods would have been well known in the art at the time of filing. See, e.g., Example 13 at page 27 of Applicants' specification, which discloses that when HES-40 was coupled to asparaginase, about 73% of the asparaginase activity was recoverable.

Given the teachings of Applicants' specification and the knowledge in the art, a skilled artisan would have been able to make and use the presently recited conjugates with no undue experimentation, and the present claims are fully enabled. Thus, Applicants respectfully request withdrawal of this rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 37, 43, 44, 46, 50-53, and 55 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,079,337 (the '337 patent). In particular, the Examiner alleged that the '337 patent discloses hemoglobin covalently bonded to a water-soluble hemocompatible polymer such as a hydroxyalkyl starch in which the alkyl is of 2 to 4 carbon atoms, wherein the covalent bond is an amine linkage.

Applicants respectfully disagree. The '337 patent describes conjugates between hemoglobin and a water-soluble polymer having polar groups and at least one negative charge (sulfate, phosphate or carboxylate residues). The polymer is disclosed to be linked to hemoglobin via at least one ionic bond, and in addition via at least one covalent bond (*see*, e.g., the Abstract

and col. 3, line 46 through col. 4, line 5 of the '337 patent). Further, there can be more than one covalent link between the polymer and the hemoglobin. As disclosed at col. 4, lines 60-66 of the '337 patent, for example, "the hemoglobin is linked to the polymer by at least one ionic bond but, in addition, by covalent links between the polymers and hemoglobin, the number of which is critical to avoid in particular the phenomenon of intermolecular cross-linking which is detrimental to the properties of hemoglobin."

Further, col. 8, lines 11-14 of the '337 patent disclose that $-NH_2$ groups of hemoglobin can form covalent bonds via carboxylic, aldehyde, or hydroxyl groups of the polymer. Dextran is stated to be a particularly preferred polymer, and the '337 patent discloses that when dextran is used, aldehyde groups are previously formed on the dextran in amounts of 18 aldehyde groups per 100 glucosidic units of the dextran, or 14 aldehyde groups per 100 glucosidic units of the dextran (see, e.g., col. 8, lines 30-45). Col. 10, lines 40-49 suggest the introduction of such aldehyde groups into the polymer by periodate oxidation by means of $NaIO_4$. It is submitted that oxidation of a polysaccharide via strong oxidants such as $NaIO_4$ leads to oxidative ring-opening of random saccharide units within the saccharide chain, and thus the formation of dialdehydes on a multitude of sugar units within the polymer chain. This is demonstrated, e.g., by Example 1 in col. 12 of the '337 patent, in which oxidation with $NaIO_4$ led to the formation of about 18 aldehydes per 100 glucose units of dextran (col. 12, lines 53-58). Thus, the '337 patent only discloses conjugates of polysaccharide polymers having a number of aldehyde groups per polymer molecule, which are used for linking to hemoglobin. Moreover, the formation of imines and subsequent reduction to amine linkages described in the '337 patent refers to a plurality of aldehyde groups, e.g. col. 10, lines 25-27 and lines 43-49.

In contrast, the present claims are directed to conjugates in which HES is covalently linked to a protein via the terminal aldehyde group of the HES molecule and a primary amino group of the protein. Thus, there is only a covalent bond between the HES molecule and the protein, and no additional ionic bond as required in the '337 patent. In addition, there is only one covalent bond between the HES molecule and the protein, as HES possesses only one terminal aldehyde group per molecule (i.e., the aldehyde group at the reducing end of the chain). In addition, according to the '337 patent, the polymer P mandatorily contains at least one Z site

which must be able to form an ionic bond (see, e.g., col.6, line 53 to col.7, line 53). HES contains no such sites.

Taken together, since there is no mention in the '337 patent of a coupling product between the terminal aldehyde group of HES and a primary amino group of hemoglobin via only one covalent bond, and since HES bears no Z site as described in the '337 patent, the presently claimed conjugates are clearly novel over the '337 patent. Thus, Applicants respectfully request withdrawal of the rejection of claims 37, 43, 44, 46, 51-53, and 55 under 35 U.S.C. § 102(b).

CONCLUSION

Applicants submit that claims 37, 43-49, and 51-55 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $130 for the Terminal Disclaimer fee under 37 C.F.R. § 1.20(d), and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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